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Accelerated approval requirements for lurbinectedin

Despite the approval of immune checkpoint inhibitors for use in combination with chemotherapy for extensive stage small-cell lung cancer (SCLC), the disease continues to carry a poor prognosis. As such, there is an urgent need for new therapeutics. Lurbinectedin was studied in a phase 2 basket trial in several malignancies, including extensive stage SCLC.[1] Based on the surrogate endpoints of overall response rate and median duration of response, the US Food and Drug Administration (US FDA) granted accelerated approval to lurbinectedin on June 15, 2020.

In the letter granting this accelerated approval, the US FDA stated that under the Code of Federal Regulations Title, Section 314.510, PharmaMar must provide "further adequate and well-controlled clinical trials to verify and describe clinical benefit".[2] The letter noted this requirement, along with the completion date of February, 2021. The letter stated the results could be from the ongoing ATLANTIS trial, a phase 3 randomised clinical trial.

ATLANTIS was presented in September, 2021, 7 months after the final report submission deadline to the US FDA. The trial failed to meet its primary endpoint of overall survival, because patients who received lurbinectedin plus doxorubicin had a median overall survival of 8·6 months compared with 7·6 months in the control group, with a hazard ratio of 0·967 (95% CI 0·815–1·148).[3] Despite failing to show survival benefit with a confirmatory trial, the US FDA has not rescinded approval for lurbinectedin. In December, 2021, PharmaMar and Jazz Pharmaceuticals announced a new confirmatory phase 3 trial, known as LAGOON, to "secure full approval in the US".[4] According to the trial's registration information, LAGOON started in January, 2022, and estimates completion in May, 2025 (NCT05153239).

Although many contemporary cancer drug approvals are based on surrogate endpoints, the US FDA has previously rescinded accelerated drug approval when subsequent studies fail to show a benefit in overall survival. It is concerning that the US FDA has not revoked approval for lurbinectedin despite negative findings from ATLANTIS.

PharmaMar's announcement of a new confirmatory trial suggests the US FDA has given lurbinectedin a second chance. This action introduces two concerns: first, patients must wait several more years for the publication of the effect of lurbinectedin on survival; and, second, it is possible that any drug will eventually yield significant results—this is the core concern of multiple hypothesis testing. Moving forward, the oncology field should consider how many chances a drug should be given, and how long patients with cancer must wait for confirmatory survival results.

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1 Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. *Lancet Oncol* 2020; **21:** 645–54.

2 US Food and Drug Administration. Zepzelca (lurbinectedin), injection, for intravenous use. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213702Orig1s000ltr.pdf (accessed Feb 26, 2022).

3 Paz-Ares L, Ciuleanu T, Navarro A, et al. PL02·03 Lurbinectedin/doxorubicin versus CAV or topotecan in relapsed SCLC patients: phase 3 randomized ATLANTIS trial. *J Thorac Oncol* 2021; **16:** S844–45.

4 PharmaMar. PharmaMar and Jazz Pharmaceuticals announce initiation of confirmatory phase III clinical trial of Zepzelca® (lurbinectedin) for the treatment of patients with relapsed small cell lung cancer. https://pharmamar.com/en/pharmamar-and-jazz-pharmaceuticals-announce-initiation-of-confirmatory-phase-iii-clinical-trial-of-zepzelca-lurbinectedin-for-the-treatment-of-patients-with-relapsed-small-cell-lung-cancer/ (accessed Feb 26, 2022).